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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
EEFERS JR, GERALD G

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 02/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/904,992	ASHKENAZI, ET AL	
	Examiner	Art Unit	
	Gerald G Leffers Jr.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 7/12/01 as Paper No. 10, in which the then pending claims were cancelled (claims 1-38) and in which new claims were added (claims 39-52). Claims 39-51 are pending in the instant application.

Information Disclosure Statement

The information disclosure statement filed 4/11/02 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because it is directed towards a series of sequence alignments and does not indicate references that are commonly available to the public. Further, it is not clear when the cited sequences were known and available to the public. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1).

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

Claims 39-51 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Each of the claims is directed towards an isolated protein having at least 80%, 85%, 90%, 95%, 99% or 100% amino acid sequence identity to the polypeptide shown in Figure 90 (SEQ ID NO: 255 or PRO302). In addition, or alternatively, the rejected claims read on a protein having 80%, 85%, 90%, 95%, 99% or 100% amino acid sequence identity to SEQ ID NO: 255, but lacking its associated signal peptide. The isolated polypeptide can have 80%, 85%, 90%, 95%, 99% or 100% amino acid sequence identity to the extracellular domain of SEQ ID NO: 255. The isolated polypeptide can have 80%, 85%, 90%, 95%, 99% or 100% amino acid sequence identity to the extracellular domain of SEQ ID NO: 255, but lacking the associated signal peptide. In addition, the isolated polypeptide can have 80%, 85%, 90%, 95%, 99% or 100% amino acid sequence identity to the protein encoded by the coding sequence of ATCC deposit number 209485. The isolated protein can be a chimeric protein comprising the polypeptide of the invention fused to a heterologous peptide sequence (e.g. an epitope tag or an Fc region of an immunoglobulin.

SEQ ID NO: 255 appears to have been novel in the art at the time of filing. Likewise, the nucleic acid sequence disclosed by applicants as encoding SEQ ID NO: 255, SEQ ID NO: 254, likewise appears to be novel in the art. Therefore, there is no well-established utility for the claimed proteins.

The specification asserts that, based upon BLAST and FastA sequence analysis, various portions of PRO302 have significant homology with various protease proteins (page 110, top paragraph). Exactly which portions have homology to which portions of which other known proteases is not taught, however. Based upon the assertion that PRO302 comprises proteolytic activity, the specification asserts that PRO302 has utility in vivo for therapy as well as in vitro

utilities. There is no indication in the specification that the supposed protease has any *specific* target for its supposed activity (e.g. association with a particular disease or specific substrate).

It is not likely that one of skill in the art could reasonably predict based upon the primary sequence of SEQ ID NO: 255 what specific activity PRO302 may have. The relationship between the sequence of a protein and its tertiary structure (in essence the structure which defines its activity), is not well understood and is not predictable as evidenced by Berendsen (Science. 1998, Vol. 282, pages 642-643; see the entire document). This reference teaches that "Thus, one of the "grand challenges" of high-performance computer-predicting the structure of proteins-acquires much of the flavor of the Holy Grail quest of the legendary knights of King Arthur: It is extremely desirable to possess but extremely elusive to obtain." (Page 643, columns 1-2). The whole reference teaches about the unpredictability in the art concerning protein structure, and failures to make it predictable. Thus, as taught by Berendsen, it is unlikely that one could predict the structural/functional characteristics of PRO302 based upon primary sequence alone. Further supporting Berendsen's teachings, Galparin et al (Nature Biotechnology, Vol. 18, pages 609-613, June 2000; see the entire reference) teach that "sequence comparison methods, even the best ones, are of little help when a protein has no homologs in current databases or when all database hits are to uncharacterized gene products." Galperin et al disclose that "assessing the actual power of the context based method for protein function prediction requires extensive testing by labor-consuming, case-by-case, computational, and eventually experimental analysis." Attwood (Science, Vol. 290, pages 471-473, see the entire reference) also states that it is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences." It is clear from the cited references that one

cannot reliably predict based upon primary structure alone or on mere sequence homology what specific activity PRO302 might possess.

The specification does teach in Example 85 that the PRO302 protein has an effect on vascular leakage when injected into hairless guinea pigs. While the specification concludes that PRO302 protein can induce vascular permeability in the guinea pig model, it does not give the actual data or an indication of the relative activity of the PRO302 protein compared to the positive control. In addition to not providing a basis for one of skill in the art to determine the actual effectiveness of PRO302 in inducing vascular permeability, the specification does not provide a basis to envision a specific, real-world application for the asserted ability to induce vascular permeability. It is further noted that the observed activity is not unique to PRO302 in that at least one other protein and the positive control both induced vascular permeability in the guinea pig model. Based on these teachings, one of skill in the art at the time of applicants' invention would not be able to recognize a specific utility (e.g. specific proteolytic substrate) or substantial utility (i.e. not requiring additional research in order to confirm a real-world application for the claimed proteins) for the claimed proteins.

Claims 39-51 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following enablement rejection is provided in the event that the rejection outlined above under 35 U.S.C. 101 for lack of a specific and substantial or well-established utility is overcome. While it may be possible that applicants can demonstrate that the instant specification and/or prior art provides a specific and substantial or well-established utility for the claimed proteins, there remain other grounds for rejecting the instant claims under 35 U.S.C. 112 1st for lack of enablement. These additional grounds are outlined below.

Claims 39-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The nature of the invention is complex, involving the use of proteins without a well-defined function.

Breadth of the claims: The complexity of the invention is exacerbated by the great breadth of the claims, encompassing proteins with as little as 80% identity to SEQ ID NO: 255,

or portions thereof (e.g. a purported extracellular domain). This includes a very large number of proteins that do not possess the specific activity of PRO302 and for which the specification provides no teachings as to a real-world use.

Guidance of the specification: The specification teaches that the cDNA encoding PRO302 was obtained from a human fetal kidney RNA library that was probed with oligomers designed from a putative extracellular domain for a given protein (e.g. Example 1, Example 85). The specification asserts that, based upon BLAST and FastA sequence analysis, various portions of PRO302 have significant homology with various protease proteins (page 110, top paragraph). Exactly which portions have homology to which portions of which other known proteases is not taught, however. Nor is it taught what exactly are the functional domains within the PRO302 polypeptide. Based upon the assertion that PRO302 comprises proteolytic activity, the specification asserts that PRO302 has utility in vivo for therapy as well as in vitro utilities. There is no teaching in the specification that the supposed protease has any *specific* target for its supposed activity (e.g. association with a particular disease or specific substrate). The specification does teach in Example 85 that the PRO302 protein has an effect on vascular leakage when injected into hairless guinea pigs. While the specification concludes that PRO302 protein can induce vascular permeability in the guinea pig model, it does not give the actual data or an indication of the relative activity of the PRO302 protein compared to the positive control. In addition to not providing a basis for one of skill in the art to determine the actual effectiveness of PRO302 in inducing vascular permeability, the specification does not provide a basis to envision a specific, real-world application for the asserted ability to induce vascular permeability.

The existence of working examples: The only working example for PRO302 is the experiment wherein it was purportedly shown that PRO302 can induce some unspecified degree of vascular permeability in the guinea pig.

State of the art/Predictability of the art: It is not likely that one of skill in the art could reasonably predict based upon the primary sequence of SEQ ID NO: 255 what specific activity PRO302 may have. The relationship between the sequence of a protein and its tertiary structure (in essence the structure which defines its activity), is not well understood and is not predictable as evidenced by Berendsen (Science. 1998, Vol. 282, pages 642-643; see the entire document). This reference teaches that "Thus, one of the "grand challenges" of high-performance computer-predicting the structure of proteins-acquires much of the flavor of the Holy Grail quest of the legendary knights of King Arthur: It is extremely desirable to possess but extremely elusive to obtain." (Page 643, columns 1-2). The whole reference teaches about the unpredictability in the art concerning protein structure, and failures to make it predictable. Thus, as taught by Berendsen, it is unlikely that one could predict the structural/functional characteristics of PRO302 based upon primary sequence alone.

Further supporting Berendsen's teachings, Galparin et al (Nature Biotechnology, Vol. 18, pages 609-613, June 2000; see the entire reference) teach that "sequence comparison methods, even the best ones, are of little help when a protein has no homologs in current databases or when all database hits are to uncharacterized gene products." Galperin et al disclose that "assessing the actual power of the context based method for protein function prediction requires extensive testing by labor-consuming, case-by-case, computational, and eventually experimental analysis." Attwood (Science, Vol. 290, pages 471-473, see the entire reference) also states that it

is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences." It is clear from the cited references that one cannot reliably predict based upon primary structure alone or on mere sequence homology what specific activity PRO302 might possess. Therefore, determining how to use the claimed polypeptides, even those having the same activity as determined for the protein described by SEQ ID NO: 255 would have been unpredictable at the time of filing.

The amount of experimentation necessary: Given the combination of factors outlined above, it would have required undue, unpredictable experimentation for one of skill in the art to use the claimed polypeptides. For example, in order to determine whether the a polypeptide meeting the claim limitations of a given percent identity to SEQ ID NO: 255, or portions thereof, has a particular activity one would have to envision an appropriate assay and conditions for measuring the purported activity. With proteolytic activity, one of skill in the art would have to envision which possible substrate of all the possible protein substrates available and under which conditions would be likely to result in an observation of the supposed activity. One would then have to envision the appropriate reaction conditions for performing the assay (e.g. purified or unpurified protein, temperature, buffer conditions, possible co-factors, etc.). If unsuccessful in determining an activity for the claimed protein, which is likely given the combination of factors outlined above and the unpredictability of the art, one of skill in the art would then have to envision a change to the first assay conditions (e.g. different substrate, buffer composition, temperature, duration and/or completely different assay) and repeat the entire unpredictable process. Thus, it would require undue, unpredictable experimentation for one of skill in the art to use the claimed proteins having a specified percent identity to PRO302 (SEQ ID NO: 255).

Therefore, the instant specification is not considered to be enabling for the use of any of the claimed proteins.

Claims 39-44, 47-48, 50-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to polypeptides having at least 80%, 85%, 90%, 95% or 99% identity with a particular disclosed sequence (SEQ ID NO: 255) and/or to the extracellular domain of the particular disclosed sequence (SEQ ID NO: 255). The claims do not require that the polypeptide possess any particular biological activity, nor any particular conserved structure, or other distinguishing feature. Thus, the claims are drawn to a genus of polypeptides that is defined only by sequence identity. It is noted that the "extracellular" domain of the protein described by SEQ ID NO: 255 has not been described in the specification or the prior art.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in

the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116) As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO: 255, but not the full breadth of the rejected claims meets the written description provision of 35 U.S.C. 112 1st paragraph. Applicant is reminded that *Vas-Cath* makes clear that

the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 39-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 39-44, 47-48, 50-51 are vague and indefinite in that the protein identified as PRO302 appears to be a soluble protein and is not explicitly disclosed as being expressed on the surface of any cell. Accordingly, the limitation that the claimed protein comprises an "extracellular domain" is indefinite, as the art does not recognize soluble proteins as having such domains. Even if PRO302 is actually be present on the surface of a given cell, the instant specification does not provide a teaching that as to what amino acid residues of PRO302 are comprised within the "extracellular domain". Thus, the metes and bounds of "extracellular domain" are vague and indefinite on at least two grounds.

Claims 39-44, 48, 50-51 are vague and indefinite in that the metes and bounds of "the extracellular domain...lacking its associated signal sequence" are unclear. It is unclear how an extracellular domain can have a signal sequence. Signal sequences are not generally though of as part of an extracellular domain because signal sequences are cleaved from the domains in the process of secretion from the cell.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gerald G Leffers Jr.
Examiner
Art Unit 1636

Ggl
February 24, 2003